L Number	Hits	Search Text	DB	Time stamp
1	14	Ruvkun NEAR Gary	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/08/16 13:30
3	435	AFX OR FKHR	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/08/16 14:24
5	25	DAF-16 AND ELEGANS	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/08/16 14:19
4	10	DAF-16 AND (AFX OR FKHR)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/08/16 14:19
2	27	DAF-16	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/08/16 14:21
7	43	(AFX OR FKHR) AND ((glucose ADJ tolerance) OR atherosclerosis OR obesity)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/08/16 14:26
8	14	(US-6319708-$ or US-6627746-$ or US-6225120-$).did. or (US-20010016332-$ or US-20030082597-$ or US-20030096957-$ or US-20010029617-$ or US-20020037585-$ or US-20030036079-$ or US-20030190312-$ or US-20030181364-$).did. or (WO-9851351-$ or WO-9630053-$).did. or (WO-200118549-$).did.	USPAT; US-PGPUB; EPO; DERWENT	2004/08/16 14:29
-	4623	ELEGANS	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/11/13 22:12

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(FILE 'HOME' ENTERED AT 14:31:20 ON 16 AUG 2004)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, MEDICONF' ENTERED AT 14:31:35 ON 16 AUG 2004

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L1          387 S DAF-16
L2         1357 S AFX OR FKHR
L3        17014 S C. ELEGAN?
L4           31 S L2 (L) L3
L5           12 DUP REM L4 (19 DUPLICATES REMOVED)
L6           88 S L1 (L) L2
L7           34 DUP REM L6 (54 DUPLICATES REMOVED)
L8            1 S L7 AND PY<=1997
L9       331031 S (GLUCOSE TOLERANCE) OR OBESITY OR ATHEROSCLEROSIS
L10           4 S L9 (L) L2
L11           3 DUP REM L10 (1 DUPLICATE REMOVED)
L12           9 S L9 (L) L1
L13           5 DUP REM L12 (4 DUPLICATES REMOVED)
                E RUVKUN G?/AU
L14         108 S E4
L15           5 S L14 AND L1 AND L2
L16           5 DUP REM L15 (0 DUPLICATES REMOVED)
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=> d an ti so au ab pi l16 5

L16 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN

AN 1997:702845 CAPLUS

DN 128:20747

TI The Fork head transcription factor **DAF-16** transduces insulin-like metabolic and longevity signals in C. elegans

SO Nature (London) (1997), 389(6654), 994-999
CODEN: NATUAS; ISSN: 0028-0836

AU Ogg, Scott; Paradis, Suzanne; Gottlieb, Shoshanna; Patterson, Garth I.; Lee, Linda; Tissenbaum, Heidi A.; **Ruvkun, Gary**

AB In mammals, insulin signaling regulates glucose transport together with the expression and activity of various metabolic enzymes. In the nematode Caenorhabditis elegans, a related pathway regulates metabolism, development and longevity. Wild-type animals enter the developmentally arrested dauer stage in response to high levels of a secreted pheromone, accumulating large amts. of fat in their intestines and hypodermis. Mutants in DAF-2 (a homolog of the mammalian insulin receptor) and AGE-1 (a homolog of the catalytic subunit of mammalian phosphatidylinositol 3-OH kinase) arrest development at the dauer stage. Moreover, animals bearing weak or temperature-sensitive mutations in daf-2 and age-1 can develop reproductively, but nevertheless show increased energy storage and longevity. Null mutations in **daf-16** suppress the effects of mutations in daf-2 or age-1; lack of **daf-16** bypasses the need for this insulin receptor-like signaling pathway. **DAF-16** is widely expressed and encodes three members of the Fork head family of transcription factors. The DAF-2 pathway acts synergistically with the pathway activated by a nematode TGF-β-type signal, DAF-7, suggesting that **DAF-16** cooperates with nematode SMAD proteins in regulating the transcription of key metabolic and developmental control genes. The probable human orthologs of **DAF-16**, **FKHR** and **AFX**, may also act downstream of insulin signaling and cooperate with TGF-β effectors in mediating metabolic regulation. These genes may be dysregulated in diabetes.

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(FILE 'HOME' ENTERED AT 14:31:20 ON 16 AUG 2004)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, MEDICONF' ENTERED AT 14:31:35 ON 16 AUG 2004

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L1          387 S DAF-16
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L4           31 S L2 (L) L3
L5           12 DUP REM L4 (19 DUPLICATES REMOVED)
L6           88 S L1 (L) L2
L7           34 DUP REM L6 (54 DUPLICATES REMOVED)
L8            1 S L7 AND PY<=1997
L9       331031 S (GLUCOSE TOLERANCE) OR OBESITY OR ATHEROSCLEROSIS
L10           4 S L9 (L) L2
L11           3 DUP REM L10 (1 DUPLICATE REMOVED)
L12           9 S L9 (L) L1
L13           5 DUP REM L12 (4 DUPLICATES REMOVED)
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=> d an ti so au ab pi l13 5 2

L13 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:761816 CAPLUS
DN 130:29188
TI Therapeutic and diagnostic tools for impaired glucose tolerance conditions based on the dauer polypeptides and genes of Caenorhabditis elegans
SO PCT Int. Appl., 202 pp.
CODEN: PIXXD2
IN Ruvkun, Gary; Kimura, Koutarou; Patterson, Garth; Ogg, Scott; Paradis, Suzanne; Tissenbaum, Heidi; Morris, Jason; Koweek, Allison; Pierce, Sarah
AB Disclosed herein are novel genes and methods for the screening of therapeutics useful for treating impaired **glucose tolerance** conditions, as well as diagnostics and therapeutic compns. for identifying or treating such conditions. The Caenorhabditis elegans metabolic regulatory genes daf-2 and age-1 encode homologs of the mammalian insulin receptor/phosphoinositide 3-kinase signaling pathway proteins, resp. In addition, the **DAF-16** forkhead protein represents the major transcriptional output of this insulin signaling pathway. Dysregulation of the **DAF-16** transcription factor in the absence of insulin signaling leads to metabolic defects; inactivation of **DAF-16** reverses the metabolic defects caused by lack of insulin signaling in C. elegans. Finally, the C. elegans daf-7, da-1, daf-4, daf-8, daf-14, and daf-3 genes encode neuroendocrine/target tissue transforming growth factor-β type signal transduction mols. that genetically interact with the insulin signaling pathway. Metabolic defects cause by lack of neuroendocrine TGF-β signals can be reversed by inactivation of the DAF-3 transcription factor. The C. elegans daf genes are excellent candidate genes and proteins for human disease associated with glucose intolerance, e.g., diabetes, **obesity**, and **atherosclerosis**. The human homologs of these daf genes and proteins mediate insulin signaling in normal people and may be defective or mis-regulated in diabetics. Moreover, there are at least 2 classes of type II diabetics: those with defects in the TGF-β signaling genes, and those with defects in insulin signaling genes. Exemplary sequences and functional characteristics are provided for the C. elegans daf homologs of the human genes: daf-2, daf-3 (3 differentially spliced isoforms), **daf-16** (2 differentially spliced isoforms), age-1, and pdk-1 (two spliced isoforms).

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9851351	A1	19981119	WO 1998-US10080	19980515

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,

CM, GA, GN, ML, MR, NE, SN, TD, TG

US 6225120	B1	20010501	US 1997-857076	19970515
AU 9874941	A1	19981208	AU 1998-74941	19980515
AU 752962	B2	20021003		
EP 1019092	A1	20000719	EP 1998-922382	19980515
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002511747	T2	20020416	JP 1998-549639	19980515
US 2001029617	A1	20011011	US 1998-205658	19981203
US 2002037585	A1	20020328	US 2001-844353	20010427
US 2003181364	A1	20030925	US 2001-963693	20010925

L13 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:384548 CAPLUS
DN 133:39116
TI Genes and polypeptides involved in insulin signaling pathways for glucose tolerance, obesity, and longevity and their uses as therapeutic and diagnostic tools
SO PCT Int. Appl., 402 pp.
CODEN: PIXXD2
IN Ruvkun, Gary; Ogg, Scott
AB Disclosed herein are novel genes and methods for the screening of therapeutics useful for treating impaired **glucose tolerance** conditions, as well as diagnostics and therapeutic compns. for identifying or treating such conditions. The Caenorhabditis elegans metabolic regulatory genes daf-2 and age-1 encode homologs of the mammalian insulin receptor/phosphoinositol 3-kinase signaling pathway proteins, resp. Also, the C. elegans PKB kinase and AKT kinase act downstream of these genes, as their mammalian homologs act downstream of insulin signaling. The C. elegans PTEN lipid phosphatase homolog, DAF-18, acts upstream of AKT in this signaling pathway. Further, the **DAF-16** forkhead protein represents the major transcriptional output of this insulin signaling pathway. Addnl. evidence indicates that the **DAF-16**, DAF-3, DAF-8, and DAF-14 transcriptional outputs of converging signaling pathways regulate metabolism The congruence between the C. elegans and mammalian insulin signaling pathways strongly supports the contention that new genes identified in the C. elegans pathway also act in mammalian insulin signaling. Exemplary sequences and functional characteristics of the C. elegans daf genes and their human homologs are provided.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000033068	A1	20000608	WO 1999-US28529	19991202
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2001029617	A1	20011011	US 1998-205658	19981203
EP 1163515	A1	20011219	EP 1999-960641	19991202
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

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L5 ANSWER 8 OF 12 MEDLINE on STN DUPLICATE 6
AN 2000484170 MEDLINE
TI DAF-16 recruits the CREB-binding protein coactivator complex to the insulin-like growth factor binding protein 1 promoter in HepG2 cells.
SO Proceedings of the National Academy of Sciences of the United States of America, (2000 Sep 12) 97 (19) 10412-7.
Journal code: 7505876. ISSN: 0027-8424.
AU Nasrin N; Ogg S; Cahill C M; Biggs W; Nui S; Dore J; Calvo D; Shi Y; Ruvkun G; Alexander-Bridges M C
AB Insulin negatively regulates expression of the insulin-like growth factor binding protein 1 (IGFBP-1) gene by means of an insulin-responsive element (IRE) that also contributes to glucocorticoid stimulation of this gene. We find that the Caenorhabditis elegans protein DAF-16 binds the IGFBP-1 small middle dotIRE with specificity similar to that of the forkhead (FKH) factor(s) that act both to enhance glucocorticoid responsiveness and to mediate the negative effect of insulin at this site. In HepG2 cells, DAF-16 and its mammalian homologs, **FKHR**, FKHRL1, and **AFX**, activate transcription through the IGFBP-1.IRE; this effect is inhibited by the viral oncoprotein E1A, but not by mutants of E1A that fail to interact with the coactivator p300/CREB-binding protein (CBP). We show that DAF-16 and **FKHR** can interact with both the KIX and E1A/SRC interaction domains of p300/CBP, as well as the steroid receptor coactivator (SRC). A C-terminal deletion mutant of DAF-16 that is nonfunctional in **C. elegans** fails to bind the KIX domain of CBP, fails to activate transcription through the IGFBP-1.IRE, and inhibits activation of the IGFBP-1 promoter by glucocorticoids. Thus, the interaction of DAF-16 homologs with the KIX domain of CBP is essential to basal and glucocorticoid-stimulated transactivation. Although **AFX** interacts with the KIX domain of CBP, it does not interact with SRC and does not respond to glucocorticoids or insulin. Thus, we conclude that DAF-16 and **FKHR** act as accessory factors to the glucocorticoid response, by recruiting the p300/CBP/SRC coactivator complex to an FKH factor site in the IGFBP-1 promoter, which allows the cell to integrate the effects of glucocorticoids and insulin on genes that carry this site.

L11 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:384548 CAPLUS
DN 133:39116
TI Genes and polypeptides involved in insulin signaling pathways for glucose tolerance, obesity, and longevity and their uses as therapeutic and diagnostic tools
SO PCT Int. Appl., 402 pp.
CODEN: PIXXD2
IN Ruvkun, Gary; Ogg, Scott
AB Disclosed herein are novel genes and methods for the screening of therapeutics useful for treating impaired glucose tolerance conditions, as well as diagnostics and therapeutic compns. for identifying or treating such conditions. The Caenorhabditis elegans metabolic regulatory genes daf-2 and age-1 encode homologs of the mammalian insulin receptor/phosphoinositol 3-kinase signaling pathway proteins, resp. Also, the C. elegans PKB kinase and AKT kinase act downstream of these genes, as their mammalian homologs act downstream of insulin signaling. The C. elegans PTEN lipid phosphatase homolog, DAF-18, acts upstream of AKT in this signaling pathway. Further, the DAF-16 forkhead protein represents the major transcriptional output of this insulin signaling pathway. Addnl. evidence indicates that the DAF-16, DAF-3, DAF-8, and DAF-14 transcriptional outputs of converging signaling pathways regulate metabolism The congruence between the C. elegans and mammalian insulin signaling pathways strongly supports the contention that new genes identified in the C. elegans pathway also act in mammalian insulin signaling. Exemplary sequences and functional characteristics of the C. elegans daf genes and their human homologs are provided.

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PI WO 2000033068	A1	20000608	WO 1999-US28529	19991202
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2001029617	A1	20011011	US 1998-205658	19981203
EP 1163515	A1	20011219	EP 1999-960641	19991202
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

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1: Ogg S, Paradis S, Gottlieb S, Patterson GI, Lee L, Tissenbaum HA, Ruvkun G. Related Articles, Links

The Fork head transcription factor DAF-16 transduces insulin-like metabolic and longevity signals in C. elegans.
Nature. 1997 Oct 30;389(6654):994-9.
PMID: 9353126 [PubMed - indexed for MEDLINE]

2: Lin K, Dorman JB, Rodan A, Kenyon C. Related Articles, Links

daf-16: An HNF-3/forkhead family member that can function to double the life-span of Caenorhabditis elegans.
Science. 1997 Nov 14;278(5341):1319-22.
PMID: 9360933 [PubMed - indexed for MEDLINE]

3: Lee SS, Kennedy S, Tolonen AC, Ruvkun G. Related Articles, Links

DAF-16 target genes that control C. elegans life-span and metabolism.
Science. 2003 Apr 25;300(5619):644-7. Epub 2003 Apr 10.
PMID: 12690206 [PubMed - indexed for MEDLINE]

4: Ookuma S, Fukuda M, Nishida E. Related Articles, Links

Identification of a DAF-16 transcriptional target gene, scl-1, that regulates longevity and stress resistance in Caenorhabditis elegans.
Curr Biol. 2003 Mar 4;13(5):427-31.
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Regulation of aging and age-related disease by DAF-16 and heat-shock factor.
Science. 2003 May 16;300(5622):1142-5. Erratum in: Science. 2003 Jun 27;300(5628):2033.
PMID: 12750521 [PubMed - indexed for MEDLINE]

6: Tissenbaum HA, Ruvkun G. Related Articles, Links

An insulin-like signaling pathway affects both longevity and reproduction in Caenorhabditis elegans.
Genetics. 1998 Feb;148(2):703-17.
PMID: 9504918 [PubMed - indexed for MEDLINE]

7: Lin K, Hsin H, Libina N, Kenyon C. Related Articles, Links

Regulation of the Caenorhabditis elegans longevity protein DAF-16 by insulin/IGF-1 and germline signaling.
Nat Genet. 2001 Jun;28(2):139-45.
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J Mol Biol. 2001 Dec 14;314(5):1017-28.
PMID: 11743719 [PubMed - indexed for MEDLINE]

9: Murphy CT, McCarroll SA, Bargmann CI, Fraser A, Kamath RS, Ahringer J, Li H, Kenyon C. Related Articles, Links

Genes that act downstream of DAF-16 to influence the lifespan of Caenorhabditis elegans.
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PMID: 12845331 [PubMed - indexed for MEDLINE]

10: Lee RY, Hench J, Ruvkun G. Related Articles, Links

Regulation of C. elegans DAF-16 and its human ortholog FKHRL1 by the daf-2 insulin-like signaling pathway.
Curr Biol. 2001 Dec 11;11(24):1950-7.
PMID: 11747821 [PubMed - indexed for MEDLINE]

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